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SEQUENCE LISTING

#10

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<120> REDOX-STABLE, NON-PHOSPHORYLATED CYCLIC PEPTIDE INHIBITORS OF SH2 DOMAIN  
BINDING TO TARGET PROTEIN, CONJUGATES THEREOF, COMPOSITIONS AND METHODS OF SYNTHESIS  
AND USE

<130> 214683

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<150> 60/137,187

<151> 1999-06-02

<160> 19

<170> PatentIn version 3.1

<210> 1

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (1)..(1)

<223> Xaa = Gla, which is gamma-carboxy-L-glutamic acid

<220>

<221> misc\_feature

<222> (9)..(9)

<223> Tyr at position 9 is an amide, i.e. C(O)NH

<220>

<221> misc\_feature

<222> (1)..(9)

<223> Xaa (Gla) and Tyr at position 9 are bridged together, making this peptide cyclic

<400> 1

Xaa Leu Tyr Glu Asn Val Gly Met Tyr  
1 5

<210> 2

<211> 9

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (1)..(1)

<223> Xaa at position 1 is alpha-amino-adipic acid (Adi)

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (4)..(4)

&lt;223&gt; xaa at position 4 is Glu or Adi

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (9)..(9)

&lt;223&gt; Tyr at position 9 is an amide, i.e., C(O)NH

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)..(9)

&lt;223&gt; xaa at position 1 and Tyr at position 9 are bridged together, making this peptide cyclic

&lt;400&gt; 2

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Leu | Tyr | Xaa | Asn | Val | Gly | Met | Tyr |
| 1   |     |     |     | 5   |     |     |     |     |

&lt;210&gt; 3

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Synthetic

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)..(1)

&lt;223&gt; xaa is any amino acid other than Glu

&lt;220&gt;

<221> misc\_feature

<222> (9)..(9)

<223> Tyr at position 9 is an amide, i.e., C(O)NH

<220>

<221> misc\_feature

<222> (1)..(9)

<223> xaa and Tyr at position 9 are bridged together, making this peptide cyclic

<400> 3

1 xaa Leu Tyr Glu Asn Val Gly Met Tyr 5

<210> 4

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (1)..(1)

<223> xaa = Gla, which is gamma-carboxy-L-glutamic acid

<220>

<221> misc\_feature

<222> (10)..(10)

<223> Cys at position 10 is an amide, i.e., C(O)NH

<220>

<221> misc\_feature

<222> (1)..(10)

<223> xaa (Gla) and Cys are bridged together, making this peptide cycli  
c

<400> 4

Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys  
1 5 10

<210> 5

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (1)..(1)

<223> Xaa = Gla, which is gamma-carboxy-L-glutamic acid

<400> 5

Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys  
1 5 10

<210> 6

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (1)..(1)

<223> xaa = Glu(OtBu)2, which is di- tert-butoxy-gamma-carboxy-L-glutamic acid

<220>

<221> misc\_feature

<222> (3)..(3)

<223> Tyr at position 3 is modified to Tyr(tBu), which is tert-butyl-tyrosine

<220>

<221> misc\_feature

<222> (4)..(4)

<223> Glu at position 4 is modified to Glu(OtBu), which is tert-butoxy-glutamic acid

<220>

<221> misc\_feature

<222> (5)..(5)

<223> Asn at position 5 is modified to Asn(Trt), which is trytyl-asparagine

<220>

<221> misc\_feature

<222> (9)..(9)

<223> Tyr at position 9 is modified to Tyr(tBu), which is tert-butyl-tyrosine

<220>

<221> misc\_feature

<222> (10)..(10)

<223> Cys at position 10 is modified to Cys(Trt), which is trytyl-cysteine, and Cys(Trt) is connected to a resin

<400> 6

Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys  
 1 5 10

<210> 7

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (1)..(1)

<223> xaa = Gla, which is gamma-carboxy-L-glutamic acid

<220>

<221> misc\_feature

<222> (1)..(1)

<223> xaa has a ClCH<sub>2</sub>C(O)- group attached

<220>

<221> misc\_feature

<222> (9)..(9)

<223> Tyr at position 9 has a -C(CH<sub>2</sub>SH)C(O)NH<sub>2</sub> group attached

<400> 7

Xaa Leu Tyr Glu Asn Val Gly Met Tyr  
 1 5

<210> 8

<211> 10

<212> PRT

<213> Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthetic

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)..(1)

&lt;223&gt; Xaa = Adi, which is alpha-amino-adipic acid

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)..(1)

<223> xaa has a CH<sub>2</sub>CO- group attached

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (10)..(10)

&lt;223&gt; Cys is an amide, i.e., C(O)NH

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)..(10)

<223> xaa (Adi) and Cys are bridged together, making this peptide cycli  
c

&lt;400&gt; 8

Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys  
1 5 10

&lt;210&gt; 9

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;



<223> Synthetic

<220>

<221> misc\_feature

<222> (1)..(1)

<223> At position 1, Xaa = Adi, which is alpha-amino-adipic acid

<220>

<221> misc\_feature

<222> (4)..(4)

<223> At position 4, Xaa = Adi, which is alpha-amino-adipic acid

<220>

<221> misc\_feature

<222> (10)..(10)

<223> Cys is an amide, i.e., C(O)NH

<220>

<221> misc\_feature

<222> (1)..(10)

<223> xaa (Adi) at position 1 and Cys are bridged together, making this peptide cyclic

<400> 9

|     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Leu | Tyr | Xaa | Asn | Val | Gly | Met | Tyr | Cys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |

<210> 10

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)..(1)

<223> Glu has a CH<sub>2</sub>CO- group attached

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (8)..(8)

&lt;223&gt; Xaa = Nle, which is norleucine

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)..(10)

&lt;223&gt; Glu and Cys are bridged together, making this peptide cyclic

&lt;400&gt; 10

|     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Leu | Tyr | Glu | Asn | Val | Gly | Xaa | Tyr | Cys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |

&lt;210&gt; 11

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthetic

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)..(1)

&lt;223&gt; Glu at position 1 is modified to Glu(OtBu), which is tert-butoxy-glutamic acid

&lt;220&gt;

<221> misc\_feature

<222> (3)..(3)

<223> Tyr at position 3 is modified to Tyr(OtBu), which is tert-butoxy-tyrosine

<220>

<221> misc\_feature

<222> (4)..(4)

<223> Glu at position 4 is modified to Glu(OtBu), which is tert-butoxy-glutamic acid

<220>

<221> misc\_feature

<222> (5)..(5)

<223> Asn at position 5 is modified to Asn(Trt), which is trityl-asparagine

<220>

<221> misc\_feature

<222> (9)..(9)

<223> Tyr at position 9 is modified to Tyr(OtBu), which is tert-butoxy-tyrosine

<220>

<221> misc\_feature

<222> (10)..(10)

<223> xaa = Nle, which is norleucine

<220>

<221> misc\_feature

<222> (10)..(10)

<223> xaa is an amide and is attached to a resin

&lt;400&gt; 11

|     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Leu | Tyr | Glu | Asn | Val | Gly | Met | Tyr | Xaa |
| 1   |     |     |     | 5   |     |     |     |     | 10  |

&lt;210&gt; 12

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthetic

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (8)..(8)

&lt;223&gt; xaa = Nle, which is norleucine

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (10)..(10)

&lt;223&gt; cys is an amide, i.e., C(O)NH

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)..(10)

&lt;223&gt; Glu at position 1 and cys are bridged together, making this peptide cyclic

&lt;400&gt; 12

|     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Leu | Tyr | Glu | Asn | Val | Gly | Xaa | Tyr | Cys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |

&lt;210&gt; 13

&lt;211&gt; 10

&lt;212&gt; PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (8)..(8)

<223> Xaa at position 8 is Nle, which is norleucine

<220>

<221> misc\_feature

<222> (10)..(10)

<223> Xaa at position 10 is Adi, which is alpha-amino-adipic acid

<220>

<221> misc\_feature

<222> (10)..(10)

<223> Xaa (Adi) is an amide, i.e., C(O)NH<sub>2</sub>

<220>

<221> misc\_feature

<222> (1)..(10)

<223> Glu at position 1 and xaa (Adi) are bridged together, making this peptide cyclic

<400> 13

Glu Leu Tyr Glu Asn Val Gly Xaa Tyr Xaa  
1 5 10

<210> 14

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (1)..(1)

<223> Glu at position 1 is modified to Glu(OtBu), which is tert-butoxy-glutamic acid

<220>

<221> misc\_feature

<222> (4)..(4)

<223> Glu at position 4 is modified to Glu(OtBu), which is tert-butoxy-glutamic acid

<220>

<221> misc\_feature

<222> (5)..(5)

<223> Asn at position 5 is modified to Asn(Trt), which is trytyl-asparagine

<220>

<221> misc\_feature

<222> (9)..(9)

<223> Tyr at position 9 is modified to Tyr(OtBu), which is tert-butoxy-tyrosine

<220>

<221> misc\_feature

<222> (10)..(10)

<223> Xaa = Adi(OAl), which is allyloxy-alpha-amino-adipic acid

<220>

<221> misc\_feature

<222> (10)..(10)

<223> Xaa is an amide, i.e., C(O)NH

<400> 14

Glu Leu Tyr Glu Asn Val Gly Met Tyr Xaa  
1 5 10

<210> 15

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (4)..(4)

<223> Tyr at position 4 is modified to pTyr, which is phosphotyrosine

<400> 15

Lys Pro Phe Tyr Val Asn Val  
1 5

<210> 16

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (2)..(2)

<223> Tyr at position 2 is modified to pTyr, which is phosphotyrosine

<400> 16

Phe Tyr Val Asn Val  
1 5

<210> 17

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 17

Leu Tyr Glu Asn Val  
1 5

<210> 18

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (1)..(1)

<223> Xaa = Glu, which is gamma-carboxy-L-glutamic acid

<400> 18

Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys Ala Ala Val Ala Leu Leu  
1 5 10 15

Pro Ala Val Leu Leu Ala Leu Leu Ala Pro  
20 25



<210> 19  
 <211> 26  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic  
 <220>  
 <221> misc\_feature  
 <222> (1)..(1)  
 <223> Xaa = Gla, which is gamma-carboxy-L-glutamic acid

<220>  
 <221> misc\_feature  
 <222> (1)..(1)  
 <223> xaa (Gla) has a CH<sub>2</sub>CO- group attached

<220>  
 <221> misc\_feature  
 <222> (10)..(10)  
 <223> Cys is an amide, i.e., C(O)NH

<400> 19

Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys Ala Ala Val Ala Leu Leu  
 1 5 10 15

Pro Ala Val Leu Leu Ala Leu Leu Ala Pro  
 20 25